CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

STN/BLA 125084

MEDICAL REVIEW

BLA – STN 125084\0
ERBITUX (Cetuximab)

United States Food and Drug Administration (FDA)
Center for Drugs Evaluation and Research
Division of Therapeutic Biological Oncology Products

Clinical Review

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Executive Summary

I. Recommendations

A. Recommendation on Approvability

The United States Food and Drug Administration (FDA) Division of Therapeutic Biological Oncology Products review team recommends Accelerated Approval, under CFR§601.41 Subpart E, for Erbitux (cetuximab), to be used in combination with irinotecan, in the treatment of EGFr-expressing metastatic carcinoma in patients who are refractory to irinotecan based chemotherapy or as a single agent is indicated for the treatment of EGFr-expression metastatic carcinoma in patients who are intolerant to irinotecan-based chemotherapy. Confirmation of clinical benefit may be based on an analysis of the ongoing phase 3 studies.

The assessment of benefit in this application is based on the surrogate endpoint of objective response. This recommendation is based on the review of the clinical data, which shows a statistically significant improvement in tumor response and time to tumor progression for cetuximab when used in combination with irinotecan in comparison to cetuximab alone in irinotecan-refractory patients. In addition, single agent cetuximab demonstrated moderate activity (durable objective tumor responses). The populations (irinotecan-refractory and irinotecan-intolerance) for whom cetuximab is indicated have no effective alternative therapy available to them.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The following are Phase 4 Commitments under 21 CFR601.41 Subpart E, as a condition for accelerated approval of cetuximab:

1. Confirmatory studies for accelerated approval:

- Completion, analysis and study reports of the following two ongoing studies are required as demonstration of "due diligence" in the evaluation of potential clinical benefit from ERBITUX treatment. **CA225006:** "A Phase III Randomized, Open-Label, Multicenter Study of Irinotecan and Cetuximab vs. Irinotecan as Second-Line Treatment in Patients with Metastatic, EGFr-Positive Colorectal Carcinoma".

- **CA225014:** "A Phase III Randomized Multicenter Study of Cetuximab, Oxaliplatin, 5-FU, and LV vs. Oxaliplatin, 5-FU, and LV in Patients with Previously Treatment Metastatic, EGFr-positive Colorectal Carcinoma".

Additional post-marketing commitments agreed upon by FDA and ImClone Systems, Inc. are:

2. Nonclinical reproductive toxicology study (ies) of ERBITUX in a suitable animal species. These data will be required to support any potential, off-label use of large-scale clinical trials in earlier stages of cancer (i.e. the adjuvant setting), and/or in support of any future indications for ERBITUX in female patients of childbearing age.

3. Conduct a clinical study to characterize the immune response of ERBITUX using a validated immunogenicity assay(s). These data can be collected in a new study or as part of an ongoing study.

4. Conduct one or more studies in EGFr-negative patients to further evaluate and confirm the value of EGFr expression in tumor as selection criteria for ERBITUX therapy in patients with metastatic colorectal cancer.
   a. To conduct and submit the results of a Phase 2 study, enrolling 50-60 patients with refractory, EGFr-negative, metastatic colorectal cancer designed to estimate the overall response rate and duration obtained with single agent Cetuximab in this population.
   b. To submit the data and analyze the results obtained in subset of patients with EGFr-negative metastatic colorectal cancer enrolled in the protocol entitled CALGB 80203 "A Phase III Trial of Irinotecan/5-FU/Leucovorin or Oxaliplatin/5-FU/Leucovorin with and without Cetuximab (C225) for Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum.

5. Conduct a dose finding study in children and adolescents who have EGFr expressing, treatment refractory, pediatric solid tumors. Plans do conduct phase II studies in individual tumor types to determine the anti-tumor activity of ERBITUX in selected pediatric solid tumors.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Cetuximab is a chimeric anti-EGFr monoclonal antibody, which binds with high specificity and affinity to the extra cellular domain of the human EGFr. Cetuximab antagonizes activation of EGFr, resulting in inhibition of cell proliferation and other cellular functions. Nonclinical studies have shown that cetuximab affects many EGFr-mediated processes, such as regulation of the cell cycle; apoptosis, angiogenesis, tumor metastasis and DNA repair mechanisms.

An accelerated approval is sought for the combination regimen of cetuximab and irinotecan for treatment of patients with EGFr-expressing metastatic carcinoma who are refractory to irinotecan based chemotherapy.

ImClone Systems, Inc has submitted one pivotal trial, EMR-62 202-007 and two supportive studies (IMCL-CP02-9923 and IMCL-CP02-0141) for efficacy evaluation.

- EMR-62 202-007 is a multi-center, phase 2, open-label study. Patients with EGFr-expressing, metastatic colorectal cancers are randomized in a 2:1 ratio, to treatment with cetuximab plus irinotecan or to cetuximab alone. The study enrolled 329 patients and was conducted in Europe.

- IMCL-CP02-9923 is a multi-center, single arm trial of cetuximab plus irinotecan in patients with irinotecan refractory metastatic colorectal cancer. The study enrolled 139 patients and was conducted in the U.S.A.

- IMCL-CP02-0141 is a multicenter, single arm trial of cetuximab alone in patients with EGFr-expressing recurrent or metastatic colorectal cancer, who had progressive disease after irinotecan. The study enrolled 61 patients and was also conducted in the U.S.A.

Safety data on a total of 1123 patients treated in nine phase 2 studies and ten phases 1 studies was submitted for review. Clinical information from 911 patients enrolled in Phase 2 studies was used to assess the overall toxicity profile of cetuximab; this was supplemented by data from Phase 1 studies, studies conducted outside of the IND (in Europe), and studies conducted with product from an alternate manufacturing site in order to characterize unusual and serious adverse events. In the Phase 2 studies,

B. Efficacy

The FDA is recommending accelerated approval of ERBITUX based on the surrogate endpoint of objective response rate.

Pivotal Study EMR-62 202-007: 329 patients were randomized to receive ERBITUX plus irinotecan or ERBITUX monotherapy. In both arms of the study, ERBITUX was administered as a 400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicity. In the ERBITUX plus irinotecan arm, irinotecan was added to ERBITUX using the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m^2 every 3 weeks, 180 mg/m^2 every 2 weeks or 125 mg/m^2 weekly times 4 doses. The primary endpoint was response rate and the study was designed to show that the response rate with the combination was superior to the response rate with ERBITUX alone.

An Independent Radiographic Review Committee (IRC), blinded to the treatment arms, assessed both the progression on prior irinotecan and the response to protocol treatment for all patients. Efficacy was evaluated in all randomized patients (ITT) and in several pre-specified sub-populations, including two key populations:

- IRC-PD, defined as randomized patients who had received at least two cycles of irinotecan-based chemotherapy prior to treatment with ERBITUX and had independent confirmation of disease progression within 30 days of completion of the last cycle of irinotecan-based chemotherapy
- IRC-PD oxaliplatin failure defined as IRC-PD patients who had previously been treated and had progressive disease or were intolerant to oxaliplatin therapy.

The FDA reviewed the electronic datasets, case report forms and all radiographic studies from all patients designated as responders by the IRC. FDA's review of the data supports the applicant's findings. Results of the FDA review are summarized in Tables 1 and 2 below.

The objective response rates of these populations are summarized in Table 1:

Table 1: FDA Analysis of Objective Response Rates

POPULATION	ERBITUX PLUS IRINOTECAN		ERBITUX MONOTHERAPY		DIFFERENCE (95% CI[a])	
	N/N	%	N	%	%	P-value*
ITT	50/218	**22.9**	12/111	**10.8**	**12.1** (4.1 – 20.2)	0.0074
IRC-PD	34/132	**25.8**	10/69	**14.5**	**11.3** (0.1-22.4)	0.074
IRC-PD Oxaliplatin failure	19/80	**23.8**	5/44	**11.4**	**12.4** (-0.8, 25.6)	0.104

*** P-value for difference in proportions between groups obtained by Fisher's exact test (2-tailed)**

Time to progression was a secondary endpoint. Lower risk of progression with the combination compared to monotherapy was demonstrated in the ITT, IRC-PD and IRC-PD oxaliplatin failure population (Table 2)

Table 2: FDA Analysis of Time to Progression

POPULATION	ERBITUX PLUS IRINOTECAN (MEDIAN)	ERBITUX MONOTHERAPY (MEDIAN)	HAZARD RATIO (95% CI[A])	LOG-RANK P-VALUE
ITT	4.1 mo	1.5 mo	0.54 (0.42-0.71)	<0.0001
IRC-PD	4.0 mo	1.5 mo	0.52 (0.37-0.73)	0.0001
IRC-PD oxaliplatin	2.9 mo	1.5 mo	0.48 (0.31-0.72)	0.0004

[a]Hazard ratio of ERBITUX™ + irinotecan: ERBITUX™ monotherapy with 95% confidence interval.

Supporting trials:

Study IMCL-CP02-9923 included 138 patients with EGFr expressing metastatic colorectal cancer who had progressed following an irinotecan-containing regimen. Patients received ERBITUX plus the same dose and schedule of irinotecan as the patient had previously failed. Of 138 patients enrolled, 83 patients had documented progression to irinotecan as determined by an Independent

Review Committee. The irinotecan progression criteria were less stringent than that proposed for EMR-62 202-007 study, as patients were not required to have failed within 30 days of prior irinotecan therapy. In addition, collection of data confirming prior irinotecan failure was performed retrospectively, rather than prospectively. There were a significant number of protocol violations in this trial (see Section VI, C for detailed review of the trials). The overall response rate, confirmed by FDA analysis, was 15.2 % (21/138) for the all-treated population and 12.1 % (9/74) for the irinotecan failure population. The median durations of response were 6.5 and 6.7 months, respectively.

Study IMCL-CP02-0141 included 57 patients with EGFr expressing metastatic colorectal cancer who progressed following an irinotecan-containing regimen. Radiographic documentation of progression to irinotecan was not required for this study. Of 57 patients enrolled, 28 patients had documented history of progression to prior irinotecan regimen. The overall response rate, confirmed by the FDA analysis was 8.8 % (5/57) for all treated patients and 14.3% (4/8) for the irinotecan failure group.

Efficacy conclusions

EMR-62 202-007 is a well-conducted, randomized phase 2 trial in a refractory, metastatic colorectal patient population who had progressed after first line therapy. In addition to having failed 5-Fluouracil and irinotecan, 38% of the patients (124/329) had also failed second line therapy with oxaliplatin. There is no effective therapy for this patient population.

Objective tumor response was confirmed in the ITT population (22.9%). Similar response rate was confirmed in the IRC-PD (25.8%) and IRC-PD oxaliplatin refractory population (23.8%). Tumor response was also confirmed for ERBITUX monotherapy ITT population (12.1%) and other populations of interest, IRC-PD (11.3%) and IRC-PD oxaliplatin failure (12.4%). A statistically significant improvement of tumor response rate was observed in the ERBITUX and irinotecan arm in the ITT population (p-value 0.0074), however the study was not powered to detect statistical significance for the secondary populations. A statistically significant longer time to progression was observed in the ERBITUX plus irinotecan arm (median 4.1 months vs. 1.5 months, p value < 0.0001).

Both supporting trials (IMCL-CP-02-9923 and 0141) confirm that ERBITUX™ alone or in combination with irinotecan can induce responses in this refractory colorectal cancer population.

C. Safety

More than 1123 cancer patients were treated with cetuximab during its clinical development program. Clinical information from 911 patients enrolled in Phase 2 studies was used to assess the overall toxicity profile of cetuximab; this was supplemented by data from Phase 1 studies, studies conducted outside of the IND (in Europe), and studies conducted with product from an alternate manufacturing site in order to characterize unusual and serious adverse events. In the Phase 2 studies, treatment with cetuximab was either as a single agent, or in combination with chemotherapy or radiation therapy. The majority of patients in the safety database had colorectal cancer. The chemotherapeutic agent most commonly used in combination with cetuximab was irinotecan.

The most serious adverse reactions associated with cetuximab were infusion reactions, dermatologic toxicity, interstitial lung disease, fever, sepsis, kidney failure and pulmonary embolus. In general, however, patients tolerated the adverse events caused by cetuximab. In the indicated population (patients with metastatic colorectal cancer), there appeared to be a higher likelihood of adverse events in patients that received cetuximab + irinotecan relative to cetuximab monotherapy. However, since there also appears to be improved efficacy in the combination therapy, the benefits of the combination therapy would seem to outweigh the risks.

Acneform-rash skin toxicity was the most common adverse event associated with cetuximab. The reaction was described by a variety of terms (acne, rash, pustular rash, dry skin, exfoliative dermatitis, etc.), usually occurred within the first three weeks of therapy, and was often severe. Associated incidences of blephitis, cheilitis, skin ulcerations and boils were observed, and an unusual adverse event, paronychial inflammation/infection, was observed in a significant percentage of the patients who received cetuximab. In most patients there was improvement in severe skin reactions with dose reduction or cessation of Cetuximab, however even in those patients with improvement, complete resolution of toxicity did not occur prior to death or discontinuation from study. In a small number of cases, patients with severe (Grade 3) skin toxicity developed concomitant *Staph aureus* septicemia and sepsis.

Infusion reactions occurred in 19% of patient who received ERBITUX plus irinotecan and 25% of patient who received ERBITUX monotherapy, even in the presence of antihistamine prophylaxis. Occasionally infusion reactions were severe, including a report of a patient death in an ongoing study not associated with the BLA ISS population. Severe infusion reactions usually occurred at the time of first infusion of cetuximab, even while being premedicated with antihistamines. Treatment of patients with a test dose of cetuximab was found to not be predictive of occurrence of severe infusion reaction.

Pulmonary toxicity in the form of interstitial lung disease was a rare but significant toxicity associated with cetuximab. Two patients developed interstitial pneumonitis following administration of cetuximab, and one of the patients died as a result of their ILD. Two patients with pre-existing pulmonary fibrosis experienced a worsening of their disease while receiving cetuximab in a manner similar to that observed in another EGF receptor / pathway based therapy.

Diarrhea and neutropenia in the clinical studies were most often due to concomitant chemotherapy. Addition of cetuximab did not appear to worsen adverse events associated with chemotherapy, and concomitant chemotherapy treatment did not appear to impact cetuximab-associated adverse events.

There did not appear to be an influence of gender, age or race on cetuximab-induced adverse events.

D. Dosing, Regimen, and Administration

The recommended dose of ERBITUX in combination with irinotecan is an initial dose of 400mg/m^2 intravenously a 120-minutes infusion with subsequent weekly doses of 250mg/m^2 infused over 60

minutes. Premedication with an H1 antagonist (e.g. 50 mg of (diphenhydramine) should be used. Patients should be observed for at least 1 hour following infusion of ERBITUX.

In the colorectal studies submitted in this application, a 20 mg test dose was administered prior to the loading dose to all patients on day 1. Analysis of subsequent clinical data submitted to the application indicated that the test dose did not reliably identify patients at risk for severe allergic reactions. Therefore, the test dose is no longer required.

In clinical trials, the following irinotecan schedules were used in combination with ERBITUX: 350mg/m^2 every 3 weeks, 180 mg/m^2 every 2 weeks or 125 mg/m^2 weekly times 4 doses with 2 weeks rest. In the event the patient receives irinotecan on the same day, irinotecan should be administered after the 1-hour observation period following the ERBITUX infusion.

E. Special Populations

1. Effects of Age

The median age of patients on the EMR 62202-007 study was 59 years (range 39-80). Twenty-seven percent of the patients were 65 years old or older. Among the responders in the combination arm, the age range was 26 to 82, with a median of 57 years; in the monotherapy arm, the age range was 49 to 69, with a median of 61 in the monotherapy arm. There were insufficient numbers of elderly patient to determine whether the efficacy of ERBITUX differs between the elderly (≥ 65 years) and younger patients. In population pharmacokinetic analysis in approximately 900 patients, there were no differences in the pharmacokinetic profile between elderly and younger patients.

2. Effects of Sex

In the pivotal trial, 62.6% of the patients were male and 37.4 % female. Of the 50 responders in the combination arm, 36 were male and 14 female (25.2% and 18.7 %, respectively). Of the 12 responders in the monotherapy arm, 10 were male and 2 were female. In the supporting trial CP02-9923 there were 21/138 responders, 14 were male and 7 female (18.4% [14/76] and 11.2% [7/62], respectively). Definitive conclusions regarding comparability of the efficacy cannot be made given the small number of patients. In population pharmacokinetic analysis in approximately 900 patients, female patients had a 25% lower intrinsic cetuximab clearance than male patients. Based on the similar toxicity profile, dose adjustment by gender is not necessary.

3. Effects of Race

Ninety-eight percent (323/329 patients) were Caucasians in the EMR 62202-007 study, which precludes a meaningful analysis of differences in efficacy and safety by race. In population pharmacokinetic analysis in approximately 900 patients, there were no differences in the pharmacokinetic profile according to race.

4. Effects of Renal impairment

In the population PK database, there were 564 patients with normal renal function, 289 patients with mildly, 49 patients with moderately, and 4 patients with severely impaired renal function. Renal

function was used as a covariate in population PK analysis and it appeared to not have an impact on ERBITUX pharmacokinetics. The limited number of patients with renal impairment does not allow a meaningful analysis of efficacy or safety differences between patients with versus without renal impairment.

5. Effects of Hepatic impairment:

In the population PK database, there were 835 patients with normal hepatic function, 23 patients with mildly, 24 patients with moderately, and 14 patients with severely impaired hepatic function. Hepatic function was used as a covariate in population PK analysis and it appeared to not have an impact on ERBITUX pharmacokinetics. The limited numbers of patients with hepatic impairment do not allow a meaningful analysis of efficacy or safety differences between patients with versus without hepatic impairment.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Applicant's Proposed Indication(s), Dose, Regimens, Age Groups

Generic Name:	cetuximab (synonyms C225, IMC-C225, ch225)
Proposed Trade Names:	Erbitux
Pharmacological Category:	Antineoplastic agent
Drug Class:	chimeric mouse/human monoclonal antibody
Route of Administration:	Intravenous
Dose and regimen:	Cetuximab 400mg/m^2 loading dose IV infusion over 120 minutes, followed by weekly 250mg/m^2 loading dose IV infusion over 60 minutes.
Population studied:	Patients with EGFr-positive metastatic colorectal carcinoma that is refractory to an irinotecan-containing regimen

C. State of Armamentarium for Indication

Colorectal carcinoma is the third most common cancer after prostate and lung cancer in men and after breast and lung cancer in women. It is estimated that in 2004 there will be approximately 146,900 new cases of colorectal carcinoma in the United States and approximately 56.700 deaths. Colorectal carcinoma accounts for approximately 10% of cancer-related mortality in the United States[1]. The primary therapy for colorectal cancer is surgical resection. Almost 50% of the cases will recur after initial surgery, in addition, 10-15% of the patients will already have metastatic disease at the time of presentation. The 5-year survival rate for patients with metastatic colorectal cancer is 5%[2].

Following are the FDA Approved Drugs for the treatment of colorectal cancer[3]:

First-line treatment for metastatic carcinoma:

- 5-FU and LV
- Irinotecan (Camptosar) with 5-FU and LV
- Capecitabine (Xeloda) when treatment with fluoropyrimidine alone is preferred
- Oxaliplatin (Eloxatin) with 5-FU and LV

Second-line treatment for metastatic carcinoma after 5-FU based therapy:

- Irinotecan (Camptosar)

Third-line treatment for metastatic carcinoma:

- Oxaliplatin (Eloxatin) with 5-FU and LV

The regimen of 5-fluorouracil and Leucovorin was the standard treatment for patients with advanced colorectal cancer in the early 1990s. In June 1996, irinotecan received accelerated approval for the treatment of recurrent or progressive colorectal carcinoma following 5-FU therapy. Approval was based on objective tumor response documented in 12.5% (95% C.I., [8.8-16.2]) of the 304 patients treated with irinotecan in three phase II studies. Conversion to regular approval was granted on October 1998, based on two large, randomized phase 3 studies that showed evidence of a survival advantage favoring irinotecan compared to best supportive care (study V301, median survival 9.2 vs. 6.2 months, $p<0.0001$, H.R. 1.76, 95% C.I. 1.31-2.36) and infusional 5-FU treatment (study V302, median survival 10.2 vs. 8.4 months, $p<0.04$, H.R. 1.37, 95% C.I. 1.02-1.85). The recommended regimens of irinotecan given as single-agent are 125 mg/m^2 weekly for 4 weeks then 2-wk rest or 350 mg/m^2 once-every 3 weeks.

On October 1999, the FDA granted regular approval for a supplemental indication for the use of irinotecan as component of first-line treatment of patients with metastatic colorectal carcinoma. Data from two large, randomized and controlled studies showed advantages in overall survival of irinotecan + 5FU/LV combinations compared with 5FU/LV alone. Study 0038 (U.S.) was a three-arm trial comparing irinotecan + 5-FU/LV weekly x 4 (Saltz Regimen), 5-FU/LV daily x 5 (Mayo Clinical Regimen), and irinotecan alone. The median survival was 14.5 vs.12.6 vs. 12.0 months respectively, with a p value of 0.042 in favor of Saltz regimen. This finding was supported by significant differences in favor of the irinotecan combination regimens in TTP ($p=0.004$) and response rate ($p<0.001$). Study v303 (Europe) compared two infusional regimens of 5-FU/LV (de Gramont and AIO regimen), with or without irinotecan. This study was designed to compare the combined results from both of the irinotecan combination arms with the combined results from both infusional 5FU/LV arms. In this analysis there was also a significant survival, TTP and RR advantage for the irinotecan combinations (median survival 16.8 vs. 14.0 months, $p=0.032$, TTP $p=0.001$, RR $p<0.005$).

On August 2002, Oxaliplatin in combination with 5-FU/LV received accelerated approval for the treatment of metastatic colorectal patients who recurred or progressed after 5-FU/LV and irinotecan therapy. Approval was based on the results of a single, multicenter, randomized study (EFC4584) comparing 5-FU/LV (de Gramont regimen, Arm A) x Oxaliplatin alone (Arm B) x Oxaliplatin, 5-FU-LV every 2 weeks (FOLFOX4 regimen, Arm C). An improvement in response rate for the combination regimen of oxaliplatin and infusion 5-FU/LV, over that of single agent oxaliplatin or 5-FU and LV was noted 0 % [0 – 2.4] for 5-FU/LV vs. 1% [0.2 – 4.6%] for oxaliplatin alone vs. 9 % [4.6-14.2] for combination Oxaliplatin, 5-FU/LV]. The p value for Arm A vs. Arm C was 0.0002. Median time to progression (TTP) was 2.7 vs. 1.6 vs. 4.6 months respectively. An improvement in TTP of almost 2 months was observed for the oxaliplatin combination Arm C over the 5-FU and LV control arm A (p value < 0.0001).

Oxaliplatin in combination with infusional 5-FU/LV received approval for the initial treatment of advanced colorectal cancer on January 9, 2004. Safety and efficacy were demonstrated in one multi-center, randomized controlled clinical trial. The oxaliplatin plus infusional 5-FU/LV regimen was compared to irinotecan plus bolus 5-FU/LV in 531 patients previously untreated for advanced or metastatic colorectal cancer. The oxaliplatin/5-FU/LV arm showed superior survival when compared with irinotecan/5-FU/LV arm with median survivals of 19.4 and 14.6 months ($p=0.0001$), respectively. Time to tumor progression and tumor response rate were also superior on the oxaliplatin plus infusional 5-FU/LV regimen.

There is no standard salvage treatment for patients in whom 5-FU, irinotecan and oxaliplatin based chemotherapy has failed.

D. Important Milestones in Product Development

The IND 5804 for ERBITUX was initially filed on October 18, 1994.

In the years of 2000 and 2001, meetings were held between ImClone Systems, Inc and the Division of Clinical Trial Design and Analysis, CBER to discuss the clinical development plan of ERBITUX for colorectal cancer and regarding the adequacy of the single arm phase trial IMCL-CP-02-9923 to support a license application.

Excerpts from clinical development plan for cetuximab meeting – August 11, 2000

- *Regarding CP02- 9923 design issues:*

- *This is a Phase 2 open label study of cetuximab plus irinotecan in metastatic or recurrent colorectal cancer refractory to irinotecan. Following two courses of irinotecan, patients' tumors are measured and based on the results, divided into the Stable Disease Treatment Group (tumor volume change< 25%) or the Progressive Disease Treatment Group (tumor > increased in volume 25%). Patients then receive irinotecan plus cetuximab until treatment failure.*

- *FDA expressed concern that because the study is a single arm trial, the effect of cetuximab plus irinotecan versus continued therapy with irinotecan alone will be unknown. To meet the standards for accelerated approval, the sponsor would have to demonstrate documentation of irinotecan failure. How many patients would fit into a stricter definition of refractory as having progressed with in a short defined period of time starting from the beginning of therapy? ImClone replied that most of the patients would fit within this definition and that they will provide data on this. They will be documenting irinotecan failure. Patient CT scans will be digitized and the REC will review the images*

- *ImClone verified that the dose(s) of irinotecan would be recorded for all patients. FDA wants to be sure that patients receive adequate doses of irinotecan and that if for some reason a lower dose is given, the reason (e.g., toxicity) is documented.*

- *FDA asked whether or not it is general practice to discontinue irinotecan after two cycles if the patient doesn't respond? The sponsor clarified that as long as a patient has stable disease and acceptable toxicity, irinotecan is continued.*

- *The FDA stated that the basic trial design is probably acceptable, but that we are not sure how the data on the stable disease patients can be used. FDA noted that there are similarities in the regulatory issues facing cetuximab compared to irinotecan, which was approved by CDER. CBER will discuss the irinotecan approval decision process with CDER to determine what criteria were used for the definition of "failure of prior chemotherapy"*

and what studies were conducted and submitted in support of that application and approval. FDA strives to apply approval criteria uniformly, if possible.

Excerpts from a teleconference regarding the ERBITUX™ clinical development plan for colorectal cancer – January 26, 2001

- *ImClone stated that ...they have never done a single agent trial of Cetuximab in colorectal cancer. A single agent trial of Cetuximab in 55 patients with renal cancer was performed and no responses were observed.*

- *Dr. Keegan advised the sponsor that for the proposed BLA to be filable, it would need to contain data on the safety and effectiveness of the combination of Cetuximab and irinotecan. It is necessary to demonstrate the contribution of each component. At the meeting on August 11, 2000, when ImClone stated that Cetuximab alone was inactive, the FDA believed that there was actual data to support this statement. However, in re-assessing the IND, the FDA found that the IND does not contain data, which would support this assertation, and we are concerned that no such data exist. Dr. Keegan also stated that an advisory committee would likely reject the reasoning that if Cetuximab alone had no effect in renal cancer, than it would also have no effect in colorectal cancer. If ImClone does not have the preclinical data to demonstrate that both Cetuximab and irinotecan contribute to the overall effect, then a randomized clinical trial of Cetuximab versus Cetuximab plus irinotecan is necessary to demonstrate that synergy is present.*

On January 12, 2001, ERBITUX™ was granted fast-track designation for the development plan that included the investigation of ERBITUX™ in combination with irinotecan for its effects on durable tumor responses in patients with metastatic colon cancer who are refractory to standard chemotherapy, where refractory is defined as progressive disease during at least 2 cycles of standard doses of 5-FU and irinotecan.

A Biological License Application was submitted for ERBITUX™ as BLA # STN 125033/0/0 on October 31, 2001 for the treatment of EGFr-positive colorectal cancer, in combination with irinotecan, that is refractory to an irinotecan-containing regimen. Data from two single arm studies, i.e. IMCL-CP-02-9923 (single arm of cetuximab plus irinotecan in patients with irinotecan refractory metastatic colorectal cancer, N=139) and IMCL-CP-0141 (single arm or cetuximab alone in patients metastatic colorectal cancer patients who had progressive disease after irinotecan, N=57) were submitted. Response rate was the primary endpoint for both trials.

The review team identified several clinical and scientific deficiencies during the initial review. Based on the information submitted in the BLA, objective tumor response was observed in 27/120 patients in the CP-02-9923 trial that received cetuximab plus irinotecan (95% CI of 15.4%, 30.5%) and 6/57 patients in the CP-02-0141 trial who received cetuximab alone. Results of these two non-randomized trials, does not support the addition of irinotecan to cetuximab. In addition, the BLA did not contain data to support that patients enrolled in the CP-02-9923 had indeed failed prior irinotecan therapy. Because of these and other major deficiencies, the

application was deemed incomplete and a Refuse to File letter was issued on December 28, 2001.

Excerpts from the RTF letter – December 28, 2001

- *The application is scientifically incomplete, in that it does not contain the data needed to evaluate the clinical effectiveness of your product.*
    - *The application does not contain data that isolates the contribution of irinotecan to the combination regimen. In order for your application to be considered complete, you were informed during the meeting of August 11, 2000, in our letter of January 19, 2001, and during the telephone conference call of January 26, 2001, that the application must provide evidence that the addition of a toxic agent (irinotecan) is necessary to achieve the clinical effect. Based on the summary information provided, and assuming that the results can be confirmed, the data do not show that the response rate observed with the combination of Cetuximab and irinotecan could not also be observed with single agent Cetuximab at the dose and schedule proposed. Your report on study CP02-9923 indicates that an objective response was observed in 27 of 120 patients who received Cetuximab plus irinotecan (95% confidence interval of 15.4%, 30.5%). Conversely, your report for study CP02-0141, states an objective response was observed in 6 of 57 patients treated with Cetuximab alone (95% confidence interval 4%, 21.5%).*

- *You must provide evidence in support of this application, which isolates and establishes the individual contributions of irinotecan and Cetuximab. Because we also have determined that the current study was not adequate and well controlled (as discussed below) and that robustness of the overall response rate is less than is stated in the study reports, you will need to conduct additional studies to provide this evidence. The most appropriate clinical study design for this purpose is a randomized controlled trial directly comparing the efficacy of single agent Cetuximab to the combination Cetuximab plus irinotecan in patients who can be documented to be refractory to irinotecan therapy. Alternatively, irinotecan therapy could be included as a third arm in a study enrolling patients who are not refractory to irinotecan.*

- *The application does not contain the data requested to support the proposed dose and schedule of Cetuximab.*

- *You have not provided data to confirm that all subjects enrolled in CP02-9923 were unresponsive or refractory to irinotecan.*

- *The application is scientifically incomplete, because the data provided to evaluate the clinical effectiveness of your product are not derived from an adequate and well-controlled study. Our preliminary review of the application has identified deviations from the protocol in a substantial proportion of subjects*

- *The presentation and organization of data for the primary efficacy analysis in CP02-9923 cannot be reviewed because of the extent of the discrepancies across datasets, as well as of the missing and incorrect information.*

- *The safety database is not complete and contains inconsistencies and discrepancies that preclude an accurate assessment of the toxicity profile.*

On February 26, 2002 a meeting was held between FDA, ImClone Systems Inc. and its corporate partners, Bristol-Myers Squibb and Merck KGaA regarding the issues relating to the December 28, 2001 Refusal to File letter and possible pathway for a resubmission of the BLA.

Prior to the meeting, ImClone disclosed to the FDA that its corporate partner Merck KGaA was conducting study a Phase 2, randomized study in patients with EGFr-expressing, metastatic colorectal cancers to treatment with cetuximab plus irinotecan or to cetuximab alone in Europe. The prospect of submitting the data from the EMR-6202-007 study to support licensure was discussed.

Excerpts from the February 26, 2002

- *The FDA clearly stated to ImClone that reanalysis of the data from CP02-9923 would not be sufficient to address the deficiencies in this application. This conclusion is based upon a determination that there are significant design and conduct flaws in the study that cannot be fully addressed by sending missing data. Data from an additional trial or trials that are adequate and well controlled are necessary.*

- *The FDA agrees that a proposal to collect additional data and conduct a reanalysis of CP02-9923 may make the data more useful...*

- *The FDA explained its position regarding the need for information about whether the use of irinotecan is needed in conjunction with Cetuximab. If the combination at some point has been shown to represent a substantial advance over available therapy and to have acceptable toxicity, ImClone may receive a license for Cetuximab for use in combination with irinotecan based upon sufficient information regarding the contribution of irinotecan to support labeling for the combination. While the best way to provide such information would be a trial showing that Cetuximab plus irinotecan is superior to Cetuximab alone, there is not an absolute requirement for such a trial for licensure. In some cases, the need for both agents of a combination may be established based upon mechanistic arguments and/or animal data. In this case, however, as noted in the past, the Agency stated that it has not found the animal data and mechanistic arguments submitted convincing and the clinical data to date do not support the argument of an absolute need for irinotecan. Additionally, the Agency pointed out that irinotecan has substantial toxicity and its use in irinotecan resistant patients as proposed by ImClone should be supported by strong evidence. Depending on the details of its design and results, study EMR-007, while not adequately powered to detect clinically important differences between monotherapy and the combination, may address this concern*

adequately for licensing in one of two ways. It may establish the safety and efficacy of Cetuximab monotherapy; or, it may, though not providing the need for irinotecan, provide sufficient supportive information in conjunction with mechanistic and animal data to be submitted, to support labeling for use of the combination.

- *Regarding ImClone's proposal to provide data from a randomized, Phase 2, European study (EMR-007), conducted by Merck, which compares Cetuximab plus irinotecan to Cetuximab alone, FDA stated that based on the protocol synopsis that ImClone provided ... EMR-007 has the potential to be used in conjunction with CP02-9923 and CP02-0141 in support of licensure....*

- *Data correlating the dose selected with clinical outcome and tumor saturation is necessary for filing the BLA.*

- *ImClone was asked to provide a detailed plan for reanalysis of CP02-9923 and CP02-0141 and to submit the complete Merck protocol EMR-007 and the statistical analysis for review.*

Between February 2002 and June 2003 several meetings were held to provide guidance and reach an agreement regarding the BLA submission.

These guidance include, but are not limited to, clear and detailed definitions for:

1. Criteria and information necessary for the determination of refractoriness to irinotecan at baseline
2. Criteria for response assessment (modified WHO criteria)
3. Population of interest for the determination of effectiveness
4. Analysis and presentation of the efficacy and safety data.

On June 5th, 2003, a pre-BLA meeting has held between FDA, ImClone Systems and its corporate partners, Bristol-Myers Squibb and Merck KGaA. The FDA agreed with the Applicant that:

1. The results from EMR 62 202-007 could form the basis for a re-submission for the BLA to support an accelerated approval of cetuximab for the proposed indication. The reanalyzed results of studies IMCL-9923 and IMCL-0141 would be included in this re-submission as supportive studies.
2. The applicant's ongoing trials in advanced colorectal cancer (CA225006 and CA225014) fulfill the requirements in 21 CFR 601.41 subpart E for confirmatory trials to support an accelerated approval of cetuximab in combination with irinotecan in the treatment of advanced colorectal cancer
3. The FDA agreed that the additional data and information to be submitted in the BLA (based on the proposal in the pre-meeting package) would address the issues raised in the December 28, 2001 Refusal to File letter.

D. Other Relevant Information

As of January 4, 2004, ERBITUX was granted approval for marketing in Switzerland, and is pending approval by the European Union (EU).

E. Important Issues with Pharmacologically Related Agents

There are no EGF receptor monoclonal antibodies approved by the US FDA.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Chemistry

Cetuximab is a human/mouse chimeric monoclonal antibody of the IgG1 subclass that binds with high affinity to the human epidermal growth factor receptor (EGFr). [redacted] The antibody chains contain the functional binding domain of murine antibody M225 to the human EGFr. [redacted]

EGFr signaling pathways are involved in the control of cell proliferation, cell survival, cell migration and cellular invasion and metastasis[4-8]. Expression of EGFr and its cognate ligand in tumors has been correlated with poor prognosis, decreased survival, and/or increased metastasis[9-11]. Cetuximab binds to the EGFr with an affinity that is approximately 5 to 10-fold higher than that of endogenous ligands. Cetuximab blocks binding of endogenous EGFr ligands resulting in inhibition of the function of this receptor. It induces internalization and down regulation of EGFr on the cell surface and has the potential to target cytotoxic immune effector cells towards EGFr-expressing tumor cells.

In preclinical studies, cetuximab inhibits the proliferation and induces apoptosis of human tumor cells that express EGFr. In vitro, cetuximab inhibits the production of angiogenic factors by tumor cells and blocks endothelial cell migration. *In vivo*, cetuximab inhibits expression of angiogenic factors by tumor cells and causes a reduction in tumor neo-vascularization and metastasis.

ERBITUX is provided in single-use vials at a concentration of 2.0 mg/mL and is formulated in a preservative-free solution containing 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42 mg/mL sodium phosphate monobasic monohydrate, 8.48 mg/mL sodium chloride and Water for Injection, USP.

B. Animal Pharmacology and Toxicology

The information in this section is obtained from the review of Dr. Anne Pilaro

Pharmacologic activity: ERBITUX was evaluated for pharmacologic activity in human tumor xenografts in nude mice and for pharmacokinetics in rats, mice, and cynomolgus monkeys.

ERBITUX binding to the EGFr competitively inhibits the binding of its normal ligands including EGF and transforming growth factor-alpha, which are implicated in tumor growth, and stimulates receptor internalization, leading to a reduction of EGFr expression on the cell surface. This antagonist action inhibits phosphorylation and activation of EGFr-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, decreased matrix metalloproteinase production, and decreased vascular endothelial growth factor production.

The epidermal growth factor receptor (EGFr) is constitutively expressed in many normal epithelial tissues. Tissue binding studies demonstrated that C225 bound to surface epithelial growth factor receptor (EGFr) present in the skin, tongue, mammary and salivary glands, ovaries, placenta, and urinary bladder of cynomolgus monkey and human tissues, and did not bind to tissues from rat, mouse, dog, or goat. Over-expression of EGFR is also detected in many human cancers including those of the colon and rectum. *In vitro* assays and *in vivo* animal studies have shown that ERBITUX, alone or in combination with irinotecan, 5-fluorouracil, or cisplatin chemotherapy inhibits the growth and survival of human tumor cells that over-express the EGFr. No anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression.

Pharmacokinetic profiles in cynomolgus monkeys following single, intravenous infusions of 7.5, 24, or 75 mg/kg or 9.84, 31, or 98.4 mg/kg cetuximab demonstrated dose-related increases in C_{max} and AUC_{last}, dose-related decreases in clearance with an increase in apparent half-life, and a volume of distribution at steady state that was approximately equal to the vascular space. On repeat administration of cetuximab at 7.5, 24, or 75 mg/kg twice weekly, toxicokinetic evaluation confirmed that exposure to C225 was continuous over the duration of the study, and that exposure to C225 was continuous over the duration of the study, with comparable values for AUC_{last} and C_{max} at the 4, 13, 26, and 39 week time points These data suggest that no significant accumulation of the antibody is occurring. Anti-cetuximab antibody development was observed in one monkey over the duration of the study, resulting in a decrease in serum C225 concentration as compared to the other animals in this dose group.

Mutagenic activity of ERBITUX was not observed in the *in vitro* bacterial reversion (Ames) assay, or in an *in vivo* mammalian micronucleus assay in rats.

Pre-clinical efficacy studies: Treatment of tumor-bearing, nude mice with cetuximab was associated with delayed tumor growth in human tumor xenografts of lung, colon, breast, or pancreatic cancers, and evidence of additive anti-tumor effects were observed when tumor-bearing mice were treated with C225 in combination with irinotecan, cis-platinum, or fluorouracil.

Pre-clinical toxicology studies: The preclinical toxicity of ERBITUX was evaluated in rats, mice, and cynomolgus monkeys.

No toxicities were observed in mice after a single dose of 300 mg C225, i/v or in Sprague-Dawley rats after single or repeated intravenous infusions of up to 40 mg /kg cetuximab twice weekly for 4 weeks.

Severe toxicities related to ERBITUX™ were observed in cynomolgus monkeys, following repeated weekly infusion of 7.5, 24, and 75 mg/kg/dose, i/v for up to 39 weeks; these doses represent approximately 0.4 to 4 times the labeled dose of cetuximab, when adjusted for total body surface area. Toxicities in this study included decreases in body weights, food consumption, anemia, decreases in leukocytes and platelet counts, alterations in menstrual cyclicity in the female animals, dose-related elevations in ALT, GLDH, and γ-glutamyl transpeptidase, and dose-dependent dermatological toxicities. Skin lesions included reddening and scale formation on the extremities, trunk, and inguinal areas, acneform pustules, hair thinning or loss, exanthema, dermatitis and wounds. These findings occurred at all dose levels of cetuximab, and were only partially reversible following interruption or discontinuation of dosing, so that no NOAEL could be defined for this ERBITUX in the preclinical safety program.

Early mortalities occurred in 5/10 monkeys that were treated with 75 mg/kg/week cetuximab beginning after approximately 12 weeks on treatment, and resulting in early discontinuation of dosing in this group after 36 weeks on study. Mortalities in the high dose animals were related to excessive dermatologic toxicity of ERBITUX following inhibition of the EGFr by cetuximab, and the subsequent defect in maturation of epidermal cells. Prior to deaths in these animals, hyper- and parakeratosis, acanthosis and acantholysis resulting in ulcerative dermatitis with desquamation of the external integument, and the epithelial mucosa of the nasal passage, esophagus, and tongue, were observed. Secondary bacterial infections of the affected skin resulted in erosive to ulcerative dermatitis, with subsequent septicemia, involvement of the major organs, and death. The dose of ERBITUX at which these early mortalities occurred was approximately 4 times greater than the clinical dose, when scaled by total body surface area.

Nonclinical safety issues relevant to clinical use: Dermatologic toxicity following ERBITUX treatment was observed both in preclinical studies in cynomolgus monkeys

after repeated, weekly treatment with the drug, and in clinical trials in patients with metastatic colorectal carcinoma. Severe erythema, skin scaling and sloughing, pustule formation, infections, sepsis, and death in 5/10 monkeys at the highest dose group were observed in animals treated with 7.5, 24, or 75 mg/kg/week cetuximab, and were only partially reversible in the highest dose group at 9 weeks after discontinuation of the biologic. Acneform rash and other dermatologic toxicities were observed clinically, and were generally Grade 2-3 in severity, and occasionally resulted in either dose reduction or dose interruption until resolved. Three clinical cases of sepsis were reported in the pivotal clinical study, with no fatalities. The potential for ERBITUX to induce severe dermatologic toxicity is related to its mechanism of action, through inhibition of critical cellular pathways associated with activation of the EGFr and subsequent epithelial cell maturation. Dose modification in case of acneform rash is provided in the package insert for ERBITUX. Additionally, the dermatologic toxicities, sepsis, and deaths in the animals will be identified in the label under the WARNINGS section; recommended language for inclusion in the label is provided in Appendix I, below.

Clinical toxicities not predicted by the animal studies included severe infusion reactions, which were characterized by rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and hypotension and were reported for approximately 3% of the patients in the phase 3 clinical study. Death secondary to severe infusion reaction occurred in one subject enrolled in the clinical study. In 90% of the incidences, the infusion reactions occurred on the first infusion of ERBITUX. No similar airway reactivity or hypotension findings were observed in the cynomolgus monkey toxicity study, after either single or repeated cetuximab infusion of up to 4 times the clinical dose, when scaled by total body surface area. The infusion reactions have been identified in a black box WARNING in the label, as well as in the WARNINGS section of the package insert.

Pulmonary toxicities not observed in the cynomolgus monkey studies included severe interstitial lung disease, and interstitial pneumonitis resulting in death in 3 and one, respectively, of 633 patients with advanced colorectal cancer during ERBITUX treatment. An additional case of interstitial pneumonitis was reported in a patient with head and neck cancer, treated in an investigative study with cetuximab in combination with cisplatin. The onset of symptoms occurred between the fourth and eleventh doses of treatment in all reported cases. There were no effects of ERBITUX treatment on respiratory safety pharmacology in cynomolgus monkeys. Additionally, no histopathological evidence of either interstitial lung disease or pneumonitis was observed in the lungs of cynomolgus monkeys treated for up to 39 weeks with cetuximab at doses of 0.4 to 4 times the clinical dose, as scaled by total body surface area.

III. Human Pharmacokinetics and Pharmacodynamics

The information in this section is obtained from the review of Dr. Hong Zhao.

A. Pharmacokinetics

Pharmacokinetics were evaluated when ERBITUX was administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy.

Single-Dose PK Parameters at Various Dose Levels: The pharmacokinetics of cetuximab after single doses ranging from 5 to 500 mg/m^2 have been characterized in a broad range of studies and tumor types. Cetuximab exhibits nonlinear pharmacokinetics. $AUC_{0-\infty}$ increased in a greater than dose proportional manner while an apparent linear relationship between cetuximab dose and mean C_{max} was observed; clearance (CL) decreased and half-life increased with increasing of doses. As the dose of cetuximab increased from 20 to 200 mg/m^2, the clearance decreased from 0.08 to 0.02 L/h/m^2 and the half-life increased from 33 hours to 80 hours. At doses greater than 200 mg/m^2, CL appeared to become constant. This plateau may be suggestive of a second, linear elimination pathway that becomes pronounced at doses above 200 mg/m^2. The volume of distribution was observed to be independent of dose and consistent with a distribution of cetuximab in the vascular space of 2-3 L/m^2.

Multiple-Dose PK: After administration of the target dose of 400 kg/m^2 initial and 250 mg/m^2 weekly, cetuximab peak and trough concentration were comparable across studies. Reasonably constant cetuximab peak and trough concentrations were generally reached within 3 to 5 weeks after the initiation of treatment and were maintained during later stages of the treatment without any accumulation.

Drug Metabolism and In vitro Drug-Drug Interaction: No studies on the metabolism of cetuximab have been performed in humans or in animals. Metabolism studies are not generally performed for monoclonal antibodies because they are proteins, which are degraded into amino acids that are then recycled into other proteins. Several pathways have been described that may contribute to antibody metabolism, all of which involve biodegradation of the antibody to smaller molecules, i.e., small peptides or amino acids. This distinction in approach to metabolism studies between small molecules and proteins is reflected in ICH Topic S6 (Note for Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, dated July 16, 1997), where it is stated, "the expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids" and that therefore classical biotransformation studies as performed for pharmaceuticals are not needed. No *in vitro* drug-drug interaction studies have been performed since P_{450} enzyme system is not expected to play any role in cetuximab biotransformation.

Rationale for Dose Selection: In the early dose-escalation studies examining doses between 5 and 500 mg/m^2, an acceptable safety profile was seen up to and including a 400 mg/m^2 weekly dose. Doses of 500 mg/m^2 produced an unacceptable high incidence of skin toxicity. A pharmacodynamic analysis of cetuximab on EGFR protein demonstrated maximal inhibition of EGFr expression across the 250-500 mg/m^2 dose range. At doses below 250 mg/m^2, however, an

increase in EGFr protein expression was observed, suggesting that therapeutic activity would be best maintained with dose at or above 250 mg/m^2. An initial dose of 400 mg/m^2 followed by a weekly dose of 250 mg/m^2 was demonstrated to be well tolerated and efficacious across multiple studies. The pharmacokinetic behavior of cetuximab together with its pharmacodynamic activity on the EGFr is further supportive of both dose and regimen.

Pharmacokinetics in Special Populations: No formal clinical studies in patients with hepatic impairment, renal impairment or in pediatric populations were conducted. A population PK analysis was conducted to investigate the potential effects of selected covariates including, hepatic and renal function, gender, race, weight, body surface area, and age on cetuximab pharmacokinetics. Female patients had a 25% lower intrinsic cetuximab clearance than male patients. Similar efficacy and safety were observed for female and male patients in the clinical trials; therefore, dose modification based on gender is not necessary. None of the other covariates explored appeared to have an impact on cetuximab pharmacokinetics

Inter-Individual Variability in PK Data: The integrated PK analysis investigated the inter-individual variability associated with the PK data. The population PK analysis identified gender as the only covariate, although this covariate did not require dose adjustment. The interpatient variability in the pharmacokinetic parameter estimates was low and ranged from 6 to 40%.

Drug-Drug Interaction: A formal drug-drug interaction study of cetuximab and irinotecan was performed and it did not reveal any evidence of a PK interaction between these two agents. In addition, the possible impact of radiation, cisplatin, paclitaxel, doxorubicin, gemcitabine, and irinotecan on the PK of cetuximab was evaluated in the population PK analysis. This analysis indicated that these concomitant therapies did not have a demonstrable influence on the PK characteristics of cetuximab.

Comparability among Product Lots: The ERBITUX lots administered in each of the studies was included in the dataset for population PK analysis. Different lots by different manufacturing processes appeared to not influence the resulting pharmacokinetics. But the lots manufactured in BB36 site, which were not included in this analysis showed pharmacokinetically noncomparable to clinical lots manufactured in Lonza facility with 26% higher trough concentration and 52% higher peak concentrations. Lots manufactured at the BB36 site were not used in the major efficacy or supportive studies.

B. Pharmacodynamics

EGFr analysis in skin biopsies appeared to reveal a decrease in EGFr protein levels across the 250-500 mg/m^2 dose range, with a maximal effect reached at a dose of 400 mg/m^2. An increase in EGFr protein levels appeared to occur at the 50 and 100 mg/m^2 doses. The pharmacodynamic effects of a single dose of cetuximab on signal transduction and cell markers in skin and tumor tissues were variable and inconclusive. There were no discernible correlations between pharmacodynamic effects in skin and tumor tissue.

Exposure-Response: The potential relationship between cetuximab exposure and the EGFr status or the response was explored in patients who had colorectal cancer and received the targeted ERBITUX dose. The derived intrinsic clearance from the saturable elimination pathway was used as a surrogate for exposure. Visual inspection of the data revealed no relationship between those patients considered to have responded and those that did not and their exposure to cetuximab. Accounting for difference in cetuximab exposure by gender gave similar results. Skin rash (a major adverse event) was included, as a potential covariate (categorical variable) in the population PK analysis and there appeared to be no discernible relationship between skin rash and cetuximab systemic exposure.

IV. Description of Clinical Data and Sources

A. Overall Data

ImClone Systems Inc submitted the clinical data in electronic format. Study reports, annotated Case Report Forms (CRF), SAS data sets, copies of all radiographic images in electronic format were provided for all patients enrolled in refractory colorectal studies, EMR62202-007, CP02-9923 and CP02-0141 studies. For the phase I studies and studies in other indications included in this application, CRFs for those patients who died, discontinued due to adverse experience or who experienced a serious adverse event were provided for the phase I studies and studies in other indications included in this application (see section IV.B. Tables Listing the Clinical Trials). CRFs were also provided for patients who were the subject of an Alert/Expedited Report from ongoing studies. Additional safety information was submitted on study IMCL-0144 during the review as per pre-BLA agreement. A literature search using PubMed was performed in addition to the literature sources provided by the applicant.

B. Tables Listing the Clinical Trials

Table 3: Study of colorectal carcinoma

STUDY NO.	STUDY DESIGN	OBJECTIVE	POPULATION	N	STATUS
EMR 62 202-007	Phase II, randomized (2:1) cetuximab and irinotecan or cetuximab monotherapy	ORR (primary)	EGFr-positive metastatic CRC who progressive after an irinotecan containing regimen	329 (218/111)	Ongoing
IMCL-CP02-9923	Phase II, non randomized, single arm, cetuximab in combination with irinotecan	ORR (primary)	EGFr-positive advanced CRC, refractory to treatment with an irinotecan containing regimen	139	Completed
IMCL-CP02-0141	Phase II, single arm cetuximab monotherapy	ORR (primary)	EGFr-positive advanced CRC, refractory to treatment with an irinotecan containing regimen	57	Completed

Table 4: Pharmacokinetic and Initial Tolerability Trials

STUDY NO.	STUDY DESIGN	OBJECTIVE	POPULATION	N	STATUS
CA225004	Phase I, open-label, randomized Cetuximab	PK (primary)	EGFr-positive advanced solid tumor	39 enrolled, data available in 25	Ongoing
EMR 62 202-012	Phase I, 2-arms: Group A: cetuximab wks 2-4, irinotecan weeks 1+4; Group B: cetuximab weeks 1-4, irinotecan week 4	PK and interaction of cetuximab with irinotecan metabolites	EGFr-positive advanced solid tumor	Group A: 6 Group B: 8	Ongoing
PopPK	Integrated PK data from all studies where PK data was collected	To develop an integrated PK database	Individual study reports	906	
IMCL-CP02-0144 PK companion	Phase II, single arm Cetuximab	Serum levels of cetuximab	EGFr positive metastatic Colorectal cancer	25	Ongoing
CA225005	Phase I, dose escalation, cetuximab monotherapy	EGFr expression and saturation in skin and tumor (primary	EGFr positive advanced solid tumor	41 enrolled, data available in 33	Ongoing

Table 5: Phase I trials

STUDY NO.	STUDY DESIGN	OBJECTIVE	POPULATION	N	STATUS
IMCL CP02-9401	Phase I, dose escalation, cetuximab monotherapy	Safety	EGFr-positive advanced solid tumors	13	Completed
IMCL CP02-9502	Phase Ib/IIa, dose escalation, cetuximab monotherapy	Safety	EGFr-positive solid tumors	17	Completed
ImCl-CP02-9503	Phase Ib/IIa, cetuximab in combination with cisplatin	Safety	Stave III or IV NSCLC and SCCHN	22	Completed
IMCL-CP02-9504	Phase Ib/IIa, cetuximab in combination with Doxorubicin	Safety	Androgen-independent prostatic cancer	36	Completed
IMCL-CP02-9605	Phase I, cetuximab in combination with paclitaxel	Safety, Dose finding	EGFr-positive stage IV breast cancer	12	Completed
IMCL-CP02-9607	Phase Ib/IIa, Cetuximab in combination with radiation	Safety	Stage III, IV or recurrent SCCHN	16	Completed
IMCL-CP02-9608	Phase I, cetuximab in combination with cisplatin	Tumor saturation	EGFr-positive recurrent or metastatic SCCHN	12	Completed
IMCL-CP02-9709	Phase Ib/IIa, cetuximab monotherapy in combination with surgical resection	PK and tumor localization/receptor saturation	Previously untreated stage II-IV SCCHN	4	Completed

Table 6: Phase II trials

STUDY NO.	STUDY DESIGN	OBJECTIVE	POPULATION	N	STATUS
IMCL-CP02-9710	Phase II, cetuximab	TTP (primary)	Metastatic renal cell carcinoma	54	Completed
IMCL-CP02-9813	Phase II, cetuximab in combination with cisplatin and radiation therapy	ORR (primary)	EGFr-positive Stage III/IV or recurrent SCCHN	21	Completed
IMCL-CP02-9814	Phase II, cetuximab in combination with gemcitabine	ORR (primary)	EGFr-positive advanced pancreatic cancer	41	Completed
IMCL-CP02-9816	Phase II, cetuximab in combination with cisplatin	RR (primary)	EGFr-positive cisplatin refractory SCCHN	131	Completed
IMCL-CP02-0038	Phase II, cetuximab in combination with irinotecan, FA and 5-FU	Safety, ORR	EGFr-positive stage IV, previously untreated CRC	30	Ongoing
IMCL-CP02-0144	Phase II, cetuximab monotherapy	RR	EGFr-positive metastatic CRC who failed at least 2 chemotherapy regimens	350*	Ongoing

* Safety data from an additional 111 patients were submitted as an amendment on September 15 during the BLA review.

C. Post marketing Experience

No post marketing experience is available to date.

D. Literature Review

The applicant conducted a review of the literature and submitted an extensive reference section under each part of the BLA.

The FDA conducted a search of the literature and reviewed the submitted references. More than 11800 articles appears in the published literature for EGF receptor. Approximately 1200 of them describe monoclonal antibodies targeting EGFr (clinical and non-clinical); of these, 145 are clinically related. For colon cancer, a careful search of the literature and the submitted reference did not yield any clinical trials in patients with colorectal cancer. Trials submitted by the applicant in support of the BLA have been presented at national and international meetings, but full reports of the findings have not been published.

V. Clinical Review Methods

A. How the Review was Conducted

The efficacy review focused on the data submitted for the pivotal study EMR-62 202-02-007 and two supporting clinical trials (IMCL-CP02-9923 and IMCL-CP02-0141) for metastatic colorectal cancer in order to confirm the primary endpoint of response rates. Additional safety information was obtained from 17 additional trials (phase I, pharmacokinetic and phase II studies for other indications) provided support for safety review. Three primary reviewers were involved:

Efficacy review:	Lee Pai-Scherf, MD
Safety Review:	Mark Thornton, MD
Imaging Review:	Mary Andrich, MD

Dr George Mills was the imaging team leader.

Electronic data sets, Case Report Forms and radiographic images were used to verify the applicant's analyses and claims. Throughout the review process, consistency between SAS data set entries and CRFs was examined. Particular attention was placed upon validation of irinotecan refractoriness in the target population. Safety information from 111 patients was submitted for study IMCL-CP02-0144 as per pre-BLA meeting agreement. Additional analysis and patient information were requested to verify product safety during the review process.

B. Overview of Materials Consulted in Review

Electronic datasets from the individual studies, case report forms and radiographic images were used for efficacy and safety analyses. Additional data and analyses were requested from the applicant to complete the review.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

FDA's Division of Scientific Investigation (DSI) audited selected centers to assess data quality and integrity. Sites that accrued the largest number of patients were selected for DSI audit. Inspections were completed at the sites listed in the following table.

Table 7: Sites inspected by Division of Scientific Investigation

STUDY EMR 602-02-007				
Study site #	Investigator	City	Country	# Of Patients
600			Belgium	41
603			Belgium	29
904			Italy	24
405			France	17
Study IMCL-CP02-9923				
Study site #	Investigator	City, State	Country	# Of Patients
001	Albert LoBuglio, MD	Birmingham, AL	USA	14
502	Albert LoBuglio, MD	Decatur, GA	USA	5
060			USA	15
066			USA	17
Study IMCL-CP02-0141				
Study site #	Investigator	City, State	Country	# Of Patients
002			USA	12

DSI determined that study conduct and data quality from these sites were acceptable with the following exceptions:

EMR 62-202-007:

- Site 405 one patient did not had ECG prior to enrollment as required by the protocol,
- Site 904: One patient did not have ECG prior to enrollment, one patient had tumor response reported as PR by the Investigator and later changed to SD. Merck KGaA failed to update the database. This was corrected during the inspection. Two patients did not had ECHO performed prior to enrollment,

IMCL-CP02-9923:

- Site 066: one patient had eligibility violation (received Panorex 3 years prior to study entry), 3 patients did not had pre-treatment serum chemistry and/ or urine analysis obtained as per protocol, 2 patients signed informed consent 5 days after study entry

IMCL-CP02-0141:

- Site 002: two serious AEs (subjects ID 1123 and 1152) were not reported to the applicant and the IRB in a timely manner.

The accuracy of the data contained within the application was verified as follows:

1. Quality Assurance assessment of CRF data into SAS Reviewer data sets:

   A 100% check of all clinical data and imaging scans for responders in colorectal cancer studies EMR62 202-007, CP02-9923 and CP02-0141 was conducted. A similar review for 10% of the non-responders from these studies was also conducted. Spot checks were

made for quality of transportation of CRF data to reviewer data sets for the non-CRC Phase 2 studies as well.

There was a > 99% accuracy of data transposed to the SAS dataset with very minor discrepancies.

2. Quality Assurance assessment of correct populating of safety summary tables from SAS dataset information

Random spot checks were made for various table values in the Integrated Safety Summary Adverse Event table summaries for the Phase 2 trial dataset. Each value checked in the tables matched exactly the incidence as derived by the reviewer from the SAS dataset. Thus it was determined that the applicant's values in incidence tables in both the ISS and the proposed labeling adequately reflected trial results.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

EMR 62 202-007 was conducted in 11 European countries. The applicant asserted that the study was performed in accordance with the Declaration of Helsinki (revised version of Somerset West, Republic of South Africa, 1996. The protocol and its amendments were approved by independent Ethics Committees and by the Authorities, according to the country-specific laws.

Studies IMCL-CP02-9923, IMCL-CP02-0141 and all other trials submitted in the application were conducted in the USA. The applicant asserted that the studies were conducted in accordance with current Good Clinical practices (GCPs) and International Conference on Harmonization (ICH) recommendations, as well as all applicable local, state and federal regulations and guidelines regarding the conduct of clinical trials. The protocol, informed consent and amendments were approved by an Institutional review Board at each investigational site in accordance with United States (US) Title 21, Code of Federal Regulations (CRF), parts 56.107 through 56.115 prior to the initiation of the study.

For study IMCL-CP02-9923, patient enrollment began prior to the protocol being submitted to the FDA in violation of 21 CFR 312.30. The first patient was enrolled in September of 1999 and the protocol was submitted to the IND on October 7, 1999.

F. Evaluation of Financial Disclosure

1. For EMR 62 202-007 Study:

Financial disclosure information was not collected from EMR 62 202-007 sites prior to initiation of the study since it was not intended to be use by ImClone as part of its BLA. Once it was determined that EMR 62 202-007 would be used in the ImClone BLA, financial disclosure information was then obtained from the sites. All except 9 investigators denied disclosable interests. For these investigators, ImClone Systems Inc filed a certificate of due diligence, stating that it has not been

possible to obtain the financial information required. The applicant indicated that these sub-investigators had left the site prior to providing financial disclosure information.

2. For IMCL-9923, IMCL-0141 and all other trials submitted in the application:

A list of all clinical investigators who provided information that they had no significant proprietary interest in ImClone Systems was provided in the application in a tabular format for all 17 clinical trials conducted in USA. For 12 sub investigators involved in the IMCL-9923 trial, information could not be obtained because the Investigator left the site prior to providing financial disclosure information.

The applicant provided the following information regarding 7 investigators with a financial arrangement with or proprietary interest in ImClone System Inc. Two investigators for [redacted] had significant financial disclosure, which required closer review:

- [redacted] at the [redacted] received Supported Research Gift from ImClone Systems [redacted] with an annual compensation of $ 100,000. [redacted] recruited a total of [redacted] patients for the study. There were only [redacted] responders among [redacted] patients. These two investigational sites were inspected by DSI, which determined that study conduct and data quality from these sites were acceptable.

- [redacted] for studies [redacted] at [redacted] received a cash payment of $ 750,000.00 in [redacted] to assign all rights, title, ownership and interest in an [redacted] to ImClone Systems, Inc. If a patent is granted based on the application, then [redacted] will be paid $ 250,000.00. [redacted] accrued a total of [redacted] patients, [redacted] patients were responders as per [redacted] recruited [redacted] patients and both were responders. The [redacted] site was inspected by DSI, which determined that study conduct and data quality from this site was acceptable. The FDA imaging reviewer further confirmed responses.

Reviewer's comment: there is minimal potential for bias of clinical study results as a result of these financial interests. The primary endpoint of EMR 60202-007, IMCL-CP02-9923 and IMCL-CP02-0141 studies was tumor response, which required radiological documentation. The results were reviewed both by an Independent Review Committee and the FDA imaging reviewers. It is not expected that the financial interested disclosed here and of those who did not file financial disclosure would affect the study results.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Efficacy data from a pivotal phase 2, 2-arm, randomized trial (EMR62202-007) and two supporting single arm studies phase 2 studies (IMCL-CP02-9923 and IMCL-CP02-0141) were submitted to support the efficacy of ERBITUX in combination with irinotecan and ERBITUX monotherapy. All trials were conducted in patients with metastatic colorectal carcinoma who had failed a prior irinotecan-containing regimen. The basis for accelerated approval was durable response rates with ERBITUX alone or in combination with irinotecan.

EMR-62 202-007 randomized patients to ERBITUX plus irinotecan or ERBITUX monotherapy. Stringent criteria were applied to confirm the irinotecan refractoriness of the efficacy population. Objective tumor response was confirmed in the ITT population (22.9%). Similar response rate was confirmed in the IRC-PD (25.8%) and IRC-PD oxaliplatin refractory population (23.8%). Tumor response was also confirmed for ERBITUX monotherapy ITT population (12.1%) and other populations of interest, IRC-PD (11.3%) and IRC-PD oxaliplatin failure (12.4%). A statistically significant improvement of tumor response rate was observed in the ERBITUX and irinotecan arm in the ITT population (p-value 0.0074). The median time to progression for the ERBITUX plus irinotecan was 4.1 months compared to 1.5 month for ERBITUX monotherapy (p value < 0.0001).

Both supporting trials IMCL-CP-02-9923 and 0141 confirm that ERBITUX alone or in combination with irinotecan can induce responses in this refractory colorectal cancer population.

B. General Approach to Review of the Efficacy of the Drug

This review focused on the BLA data submitted by ImClone Systems, Inc for pivotal study EMR 62 202-007 and supporting studies IMCL-CP02-9923 and IMCL-CP02-0141. In addition to confirmation of patient eligibility, treatment and tumor response, particular attention was placed upon validation of irinotecan refractoriness in the target population. Study reports, CRF's, SAS data sets and radiographic images were used during the review process.

C. Detailed Review of Trials by Indication

1. Study EMR 620202-007

Protocol Title:
"BOND – Bowel Oncology with Cetuximab Antibody, An Open, randomized, multicenter, phase II study of cetuximab alone or in combination with irinotecan in patients with metastatic colorectal adenocarcinoma expressing the epidermal growth factor receptor (EGFr) and progressing on a defined irinotecan-based regimen"

Study sites:
The study was conducted in 56 investigational sites in 11 European countries

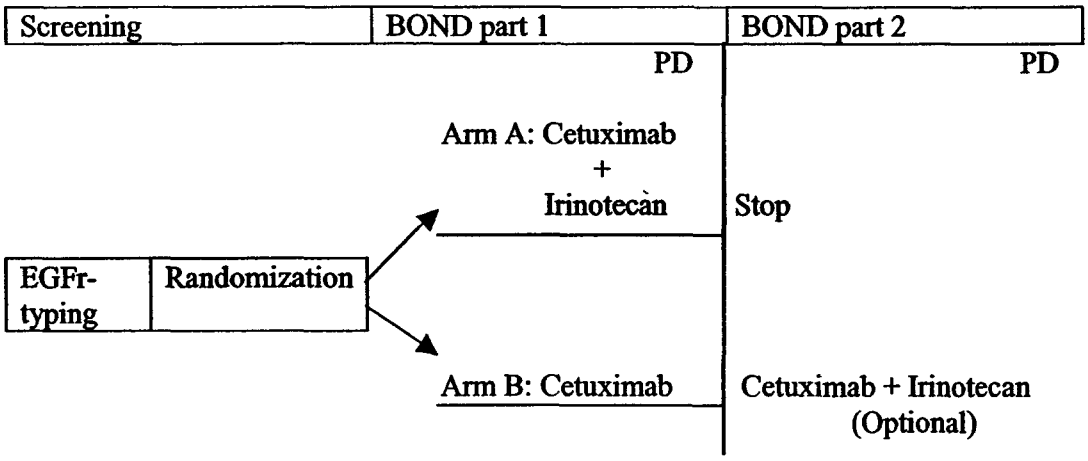
Study Period:
The study is ongoing
Date of 1st patient enrolled: July 31, 2001
Date of last patient randomized: May 13, 2002
Date of data cut-off: November 15, 2002
Date of survival data cut-off: January 31, 2003
Objectives:
Primary objective
To determine the objective confirmed response rate of the combination of cetuximab plus irinotecan and of cetuximab as a single agent in patients with metastatic colorectal cancer (CRC) who were progressive on an irinotecan-containing regimen

Secondary:

- To assess differences in efficacy between the 2 treatment groups
- To determine time to progression (TTP), time to treatment failure, duration of response, an survival time
- To determine the percentage of patients who were progression-free at 3 and 6 months
- To evaluate the safety and toxicity of cetuximab in combination with irinotecan and as a single agent
- To evaluate population pharmacokinetic parameters
- To determine response rate and disease control rate in part 2 of the study

Study design

The overall study design is summarized in the following diagram:



This was an open-label, randomized, multicenter, phase II, 2-arm study on patients with metastatic CRC whose tumors express the EGFr. In part 1 of the study, patients were randomized 2:1 to cetuximab n combination with the same dose of irinotecan to which they became refractory or to cetuximab monotherapy. Randomization was performed by minimization with the stratification factors: Karnofsky performance

status (KPS) [60 to 70 versus 80 to 100], previous treatment [after first-line treatment versus after second or subsequent treatment lines with oxaliplatin versus after second or subsequent treatment lines without oxaliplatin], and center. All patients were to be treated with study medication until progressive disease (PD) or occurrence of unacceptable toxicity. Patients with progressive disease on cetuximab monotherapy in arm B could continue cetuximab in combination with the same irinotecan regimen to which they had become refractory (part 2 of study)

Study Population
Inclusion Criteria

- Diagnosis of histologically confirmed adenocarcinoma of the colon or rectum
- Stage IV colorectal carcinoma
- Male or female ≥18 years of age
- Signed written informed consent
- Presence of at least one uni-dimensionally measurable lesion; index lesions must not be in a previously irradiated area

Reviewers comment: The FDA advised that the WHO criteria, based on sum of bi-dimensional measurement of lesions, be used. WHO criteria were adopted for the IRC in order to optimize comparability of the 007 and 9923 and 0141 studies.

- Immunohistochemical evidence of positive EGFr expression prior to study entry in primary tumor and/or at least one metastasis by the DAKO EGFr Detection System kit
- One of the following irinotecan regimens as most recent chemotherapy treatment (together with a maximum of two licensed dose reductions) for at least 6 weeks:
  - Irinotecan 125 mg/m^2 weekly for 4 consecutive weeks followed by two weeks rest, as a single agent or combined with 5-FU/FA, or
  - Irinotecan 180 mg/m^2 every 2 weeks in combination with 5-FU/FA or
  - Irinotecan 350 mg/m^2 every 3 weeks as a single agent or combined with 5-FU/FA
- Documented progression by comparison of CT or MRI scans on the defined irinotecan based therapies whereby the time between documentation of progression and randomization should not be longer than 3 months
- Karnofsky performance status of ≥60 at study entry
- Life expectancy of ≥3 months
- Effective contraception for both male and female patients if risk of conception exists
- Laboratory parameters
  - Neutrophils ≥1.5 x 10^9/L, platelets ≥100 x 10^9;/L, and hemoglobin ≥9 g/dL
  - Bilirubin level normal or ≤1.5 x uln
  - ASAT and ALAT ≤5 x uln
  - Serum creatinine ≤1.5 x uln

Exclusion Criteria:

- Brain metastasis (known or suspected)
- Surgery or irradiation with in 4 weeks prior to study entry
- Concurrent chronic systemic immune therapy, chemotherapy, or hormone therapy not indicated in the study protocol
- Any investigational agent(s) within 4 weeks prior to entry
- Previous exposure to EGF, monoclonal antibodies, signal transduction inhibitors or EGFr targeting therapy
- Clinically relevant coronary artery disease or a history of a myocardial infarction within the last 12 months
- Acute or subacute intestinal occlusion or history of inflammatory bowel disease
- Known grade 3 or 4 allergic reactions to any of the components of the treatment
- Pregnancy or breastfeeding
- Previous malignancy, with exception of a history of a previous basal cell carcinoma of the skin or pre-invasive carcinoma of the cervix
- Known drug abuse/alcohol abuse
- Legal incapacity or limited legal capacity
- Medical or psychological condition which in the opinion of the investigator would not permit the patient to compete the study or sign meaningful informed consent

Randomization:

Eligible patients were randomized in a ratio of 2:1 to Arm A (ERBITUX plus irinotecan) or Arm B (ERBITUX monotherapy). Each center called the IVRS central randomization service. Randomization was performed via a minimization dynamic allocation method with the following stratification factors:

- Karnofsky Performance Status (KPS) 60 to 70 vs. 80 to 100
- Previous treatment, patients coming from 1st line treatment vs. patients coming from 2nd or subsequent treatment line with prior oxaliplatin vs. patients coming from 2nd or subsequent treatment line without prior oxaliplatin
- Study center (56 centers)

Treatment Plan:

Patients randomized to arm A received cetuximab and irinotecan. Patients randomized to arm B received cetuximab monotherapy. Treatment was to be continued until PD or occurrence of unacceptable toxicity.

Patients were to receive cetuximab at a loading dose of 400mg/m^2 over 120 minutes and weekly cetuximab infusions at a maintenance dose of 250mg/m^2 over 60 minutes (maximum rate 10 mg/min = 5 mL/min). For safety reasons the first 20 mg of the loading dose were to be administered as a test dose over a period of minimum 10

minutes. The protocol mandated pre-treatment with an appropriate antihistamine as prophylactic treatment to avoid an allergic reaction.

Irinotecan was to be administered at the same dosage regimen on which the patients become refractory to irinotecan therapy. The following dosage regimens of irinotecan were allowed, together with the licensed dose reductions for prior irinotecan-associated toxicity:

- 125 mg/m^2 weekly for 4 consecutive weeks, followed by 2 weeks rest
- 180 mg/m^2 every two weeks
- 350 mg/m^2 every three weeks

There was to be at least one hour between the end of the cetuximab infusion and the start of the irinotecan infusion.

Dose Modifications and delays

Toxicity was graded according to the NCI/NCI Common Toxicity Criteria 2.0 and using a Merck Code.

Cetuximab

Skin toxicity:

- If a patient experienced a grade 3 skin toxicity, cetuximab therapy could be delayed for up to two consecutive infusions with no change in the dose level.
- If toxicity resolved to ≤grade 2, treatment was permitted to resume.
- With the 2nd and 3rd occurrences of a grade 3 skin toxicity, cetuximab therapy could again be delayed for up to 2 consecutive weeks with concomitant dose reductions to 200 mg/m^2 and 150 mg/m^2, respectively.
- Treatment was to be discontinued permanently if there were more than 2 consecutive infusions held or a subsequent occurrence of a grade 3 skin toxicity despite appropriate dose reductions.

Allergic reaction:

- Grade 1 or 2: cetuximab infusion rate should be decreased for subsequent infusions, but the infusion time should not exceed 4 hours
- Grade 3 or 4: cetuximab was to be stopped and patient was to be discontinued from further treatment (but followed for safety and efficacy endpoints).

Cetuximab was to be discontinued in patients who experienced any cetuximab-related grade 4 toxicity.

Cetuximab was not to be delayed for toxicities related to irinotecan.

Irinotecan

Increases of irinotecan dosage were not allowed in this study. Irinotecan was not to be withheld in case of cetuximab delays.

Dose adjustment and omissions of irinotecan were to be carried out according to the approved irinotecan (Camptosar®) Package Insert. A detailed plan for dose adjustment for hematologic and non-hematologic toxicities for each irinotecan dose schedule was submitted in the protocol.

Concomitant Treatment

Permitted medications and treatments: sedatives, antibiotics, analgesics, antihistamines, antiemetics, steroids, G-CSF and blood components

Excluded medications and treatments: chemotherapy and radiation therapy

Study Schedule (Table 8)

- Pre-screening: evaluation of EGFr status on tumor tissue (1st informed consent)
- Screening: assessment of EGFr-positive patients with documented PD on a defined irinotecan regimen or study eligibility, randomization of eligible patient to study medication (2nd informed consent)
- Treatment period: treatment with study medication until PD or unacceptable toxicity
- Follow up period: assessment of survival status.

Table 8 – Study Schedule

Study Procedure	Pre-screening	Screening (-21 d)	Weekly visit	6-wk visit	End of study	F/u q 6 wks
1st informed consent	X					
Allocation of patient number	X					
Demographics	X					
Tumor diagnosis	X					
EGFr assessment	X					
2nd informed consent		X				
Baseline screening (inclusion/exclusion criteria)		X				
Medical history		X				
Pregnancy test		X				
Physical examination		X		X	X	
Karnofsky Performance Status (KPS)		X		X	X	
ECG		X			X	
Measurement of ejection fraction		X			X	
Documentation of PD before study entry		X				
Tumor assessment (target & non-target lesions)		X		X[2]	X[4]	
Laboratory safety[3]		X		X	X	
Adverse events, concomitant medication, premature discontinuation		X	X	X	X	
Randomization		X				
Vital signs		X	X	X	X	
Cetuximab administration			X			
Irinotecan administration			X[1]			
Survival status						X

1 Irinotecan: depending on the used regimen

2 CT or MRI evaluation was to be done at baseline, week 6, 12, 18 and 24, and then every 3 months. In case of response (PR or CR) after week 24, a confirmation CT or MRI had to be performed after 4-6 weeks.

3 Hematology, biochemistry and urinalysis; hematology had to be done within 48 hours prior to administration of irinotecan.

4 CT or MRI, unless the last CT/MRI scan was performed within 4 weeks.

Progression of disease and end of study:

- Patients in arm A (cetuximab plus irinotecan): treatment was to be stopped in the event of PD. If the patient developed unacceptable toxicity to irinotecan, patient could continue with cetuximab alone until PD
- Patients in arm B (cetuximab monotherapy): in the event of PD, patients wishing to continue with the combination of cetuximab and irinotecan were permitted to continue in part 2 of the study. The same regime of irinotecan to which the patient became refractory should be added to cetuximab within 2 weeks after PD.

Follow up: survival status was to be checked every 6 weeks after the end of the study.

Study Objectives

The **primary objective** of this study was to determine the objective confirmed tumor response rate of the combination of cetuximab plus irinotecan and of cetuximab as a single agent in patients with metastatic colorectal cancer who were progressive on an irinotecan-containing regimen.

The **secondary objectives** were:

- To assess the difference in efficacy between the two treatment groups
- To determine time to progression (TTP)
- To determine time to treatment failure (TTF)
- To determine the percentage of patients who were progression-free at 3 and 6 months
- To determine the percentage of patients who were progression-free at 3 and 6 months
- To determine the duration of response (DR)
- To determine the overall survival times (OS)
- To evaluate the safety and toxicity of cetuximab in combination with irinotecan and of cetuximab as a single agent
- To evaluate population pharmacokinetic parameters
- To determine response rate and time to progression in part 2 of the study
- To investigate the inhibition of the EGFr signaling pathway in patients randomized to receive cetuximab monotherapy (Arm B) and giving additional consent to participate in these pharmacodynamic investigations (local amendment at Belgian centers)
- To determine if the activity demonstrated by cetuximab plus irinotecan could be maintained event if irinotecan was withdrawn

Tumor assessment:
The following pre-study and on-study scans were collected, digitalized and sent to [redacted]

Pre-study scan taken before or during the most recent pre-study irinotecan regimen
Pre-study scan showing progression of disease on one of the defined irinotecan regimens
Screening/base line scan prior to randomization
On study scans, taken at weeks 6, 12, 18 and 24 and every 3 months thereafter
Additional scans for confirmation of response 4 to 6 weeks after response.

[redacted] was responsible for providing the technical facilities, digitizing the scans, and organizing the independent review of CT or MRI image by the IRC.

Independent Review Committee (IRC)

Analysis of efficacy endpoints were performed using the Independent Review Committee charter for radiologic assessment of pre-study irinotecan refractoriness and response to on-study treatment. Results were analyzed according to the Statistical Assessment Plan

Both the Independent Review Committee charter and the Statistical Assessment Plan were revised and finalized on April 2, 2003.

The IRC comprised of 3 independent, board-certified radiologist of national equivalent (readers) and an oncologist who were responsible for the assessment:

- Of pre-study scans and limited clinical data to establish whether the patient had a pre-study status of PD or a pre-study status of non-PD;
- Of on-study scans and clinical data to determine the primary efficacy endpoint of best overall response date of first response, date of response, confirmation, date of progression, and date of last tumor assessment.

The IRC was blinded with regard to institution, patient identifiers, investigator's assessment of response, and treatment group. In the original protocol, the IRC was to assess tumor responses according to the RECIST criteria. The protocol was amended on July 23, 2003 to assess tumor responses according to the modified WHO criteria to optimize comparability of the results from Studies EMR-62 202-07, IMCL-CO02-9923 and IMCL-CP02-0141.

On study assessment of tumor response were based on computed tomography (CT) or magnetic resonance imaging (MRI) scans that were taken every 6 weeks. The sizes of index lesions were measured, non-index lesions were assessed, and new lesions recorded.

Criteria for tumor evaluation by IRC

The modified WHO Response Criteria use to assess tumor response by IRC are presented in Table X, and overall response for all possible combination of target, non-target and new lesions are given in Table 9.

The index lesions (maximum of 5 per often and 10 lesions in total) were selected by the radiologist. Lesions were measured in 2 dimensions with the size estimated by the product of the longest diameter and the greatest perpendicular diameter. All other lesions were to be identified as non-index lesions and documented. Lesions could be measured, but were not used in the calculation of the SOP of index lesions.

Table 9 – Criteria for Tumor Evaluation

DISEASE RESPONSE	DEFINITION
Complete response (CR)	The disappearance of all index lesions by two observations no less than four weeks apart, and no evidence of progressive disease.
Partial response (PR)	A 50% or more decrease in the sum of the products of the longest diameter and the greatest perpendicular diameter of all index lesions compared to baseline, by two observations not less that four weeks apart, and no evidence of progressive disease.
Stable disease (SD)/No change (NC)	Neither sufficient decrease to qualify for partial response nor sufficient increase to qualify for progressive disease.
Progressive disease (PD)	An increase of 25% or more in the sum of the products of the longest diameter and the greatest perpendicular diameter of index lesions compared to the smallest recorded sum (nadir) during the study, or appearance of one or more new lesions.
Duration of overall response:	The duration of response for patients with a complete or partial response is defined as the time from the first assessment of either a CR or a PR (whichever status occurs first) to first evidence of progressive disease or death.

Table 10: Overall Response for All possible Combinations of Tumor Responses

Index Lesions	Non-Index Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	NC	No	PR
PR	CR or NC	No	PR
SD	CR or NC	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Safety variables

All adverse events (AEs) regardless of whether or not they were considered to be drug related were reported. Causal relationship was to be rated by the Investigator as unrelated, possible, probable, or definite. Grading was to be assessed according to NCI, CTC, version 2.0.
Laboratory safety variables included hematology, blood chemistry, urinalysis and pregnancy tests performed as per protocol pre-specified schedule. Other safety variables included vital signs, physical examination, ECG recordings, cardiac ejection fraction (MUGA or Echocardiogram) and KPS.

Special laboratory variables

EGFr expression was determined by a standardized, immunohistochemical method (DAKO EGFr Detection System, DakoCytomation, Glostrup, Denmark) in archived tumor material or biopsies taken prior to inclusion in the study. The tumor material could be taken from the primary tumor or a metastasis. The determinations were performed centrally by a pathologist in Germany.

HACA was analyzed in the patients who had blood samples taken from HACA analysis in accordance with Amendment 3 (i.e. at least 6 weeks after the last dose of cetuximab). HACA was also determined in patients with AEs that might be indicative of an immune response, i.e. allergic reaction, anaphylactoid reactions, flu-like syndrome, chills, or grade 3 fever. HACA samples were to be collected at screening and before cetuximab administration on week 2, day 8; week 7, day 43, week 13, day 85 and end of study visit, 6 weeks after the last administration of cetuximab. Preclinical studies and preliminary clinical data from other studies suggested that cetuximab in serum interfered with the ELISA assay used to determine HACA. This issue was addressed in Amendment 3; an additional blood sample was to be taken 6 weeks after the last administration of cetuximab.

Statistical and analytical Plan

Patient populations:

The efficacy analysis was performed in the intent to treat (ITT) population and 6 sub-populations. These key populations were identified in the Statistical Analysis Plan prior to data base lock and analysis:

1. **Intent to treat (ITT)**: All randomized patients
2. **Safety population**: all patients who received any dose of cetuximab
3. **Per protocol:** All IRC-PD patients who did not had a major protocol violation, had adequate study medication compliance, i.e., received at least 50% of the scheduled cetuximab treatment (number of infusions divided by weeks of cetuximab treatment) > 0.5, had received at least 6 weeks of cetuximab treatment, except in case of death or PD within the first 6 weeks after start of cetuximab treatment.
4. **IRC PD:** All ITT patients with an objective confirmed irinotecan-refractory status:
   - Progressed on prior irinotecan as determined by the IRC
   - Progressed within 30 days after the last irinotecan treatment course, i.e., pre-study scans documenting progressive disease
     - For the 125 mg/m^2 weekly and for the 350 mg/m^2 every 3 weeks schedule: within 51 days of last dose of prior irinotecan
     - For the 180 mg/m^2 every 2 weeks schedule within 44 days of last dose of prior irinotecan
   - Pre-study comparison scan was performed either less than or equal to 6 weeks (42 days) prior to the first dose of the most recent irinotecan therapy or performed after first dose, at least four weeks prior to the date of the scan used to assess progression
   - Pre-study comparison scan/pre-study scan documenting PD: at least a 4- week interval between the 2 scans covering at least 1 course (cycle) of irinotecan therapy
   - Minimum irinotecan dosing: received adequate pre-study irinotecan

- Received any dose of cetuximab

5. **ITT oxaliplatin:** All ITT patients with prior oxaliplatin therapy
6. **IRC PD oxaliplatin:** All IRC-PD patients with prior oxaliplatin therapy

Two additional subpopulations were included in the analysis at the recommendation of the FDA to support the BLA re-submission:

1. **IRC PD oxaliplatin failure population:** all IRC-PD patients where the reason for failure of oxaliplatin treatment is either disease progression or intolerance.
2. **IRC PD-2cycle:** All IRCPD patients who had received a minimum of 2 cycles of irinotecan-based therapy.

The IRC PD-2 cycle subpopulation meets the FDA criteria for Fast Track Product development of cetuximab (January 12, 2001)

Statistical methodology and analysis:

Sample size determination
The original study was designed to enroll 225 patients, 150 in arm A (cetuximab in combination with irinotecan) and 75 in arm B (cetuximab monotherapy). Patients would have progressed while receiving or within 3 months after having received an irinotecan containing treatment regimen. On March 19, 2002, the protocol was amended to increase the sample size from 225 to 300 patients after the Swedish medical products agency determined that a patient population that fulfilled the more restrictive inclusion criterion of being progressive at most 30 days after the end of irinotecan treatment course would be considered truly refractory to irinotecan. The applicant and FDA agreed that the sample size of 300 patients would be sufficient to show that the 95% confidence interval around the differences in observed response rates between the two treatment arms excluded zero (in support of the secondary objective in amendment 1, to assess the difference in efficacy between the two treatment groups).

General methods: continuous variables were summarized using descriptive statistics. Qualitative variables were summarized by means of counts and percentages in terms of frequency tables. Two-sided Clopper-Pearson exact 95% CIs were calculated for response and disease control rates. Time-to-event variables were presented using Kaplan-Meier probabilities and curves with associated statistics, i.e., the median and two-sided 95% CI.

Amendments to protocol

Protocol issued on June 18, 2001

Amendment 1: March 19, 2002

- Issued after 208 patients were randomized.
- Increased the final sample size from 225 to 300 patients after Swedish medical products agency determined that a patient population that fulfilled the more restrictive inclusion criterion of being progressive at most 30 days after en of irinotecan treatment course would be considered truly refractory to irinotecan

- Secondary objective added to assess the difference in efficacy between the treatment groups.

Amendment 2: July 23, 2002

- Issued after all patients had been randomized, but before database lock and analysis
- Changes the criteria to be used in the assessment of the primary efficacy endpoint, tumor response, from the one-dimensional criteria of RECIST to the bidimensional criteria of the World Health Organization (WHO). This change was implemented to optimize comparability of the results from Studies EMR-62 202-07, IMCL-CO02-9923 and IMCL-CP02-0141
- EGFr expression to be presented as % of positive cells instead of positive grading.

Amendment 3: August 15, 2003

- Pre clinical and clinical studies indicated that presence of cetuximab interfered with ELISA assay to measure HACA. Protocol amended to collect blood samples at 6 weeks after the last dose of cetuximab (wash-out period)

Local Amendment (Belgium): December 14, 2001

- Amendment providing for the performance of pharmacodynamic assessment in skin biopsies obtained at a single investigation site in Belgium

RESULTS

Between July 31, 2001 and May 13, 2002, 329 patients were enrolled in 56 study sites in 11 European countries: 6 in Austria, 4 in Belgium, 7 in France, 6 in Germany, 8 in Italy, 5 in The Netherlands, 1 in Norway, 6 in Spain, 2 in Switzerland, 2 in Sweden and 9 in United Kingdom.

A total of 577 patients were screened for EGFr status. 474 (82.1%) of these patients were EGFr positive and were screened for eligibility to the protocol. A total of 329 patients were randomized to study medication: 218 to cetuximab in combination with irinotecan (arm A) and 111 to cetuximab monotherapy (arm B).

The patients were stratified according to KPS and previous therapy. The distribution of patients by stratification factors is shown in Table 11. They were similar across arms.

Table 11. Stratification and Treatment groups (ITT population)

Stratification	Cetuximab and Irinotecan N=218 (100%)	Cetuximab monotherapy N=111 (100%)	Total N=329 (100%)
Karnofsky Performance Status			
< 80	26 (11.9%)	14 (12.6%)	40 (12.2%)
≥80	192 (88.1%)	97 (87.4%)	289 (87.8%)
Previous Therapy			
First line	30 (13.8%)	17 (15.3%)	47 (14.3%)
Subsequent line with oxaliplatin	132 (60.6%)	69 (62.2%)	201 (61.1%)
Subsequent line without oxalipl	56 (25.7%)	25 (22.5%)	81 (24.6%)

One patient in each arm was randomized, but was EGFr negative; 2 patients were randomized but did not receive any study medication (603-17, died due to disease progression prior to therapy; 603-22, withdrew consent after randomization). Four patients (304-1, 401-11, 405-10, 603-29) were randomized to the cetuximab and irinotecan group, but received only 1 dose of cetuximab as a single agent due to a severe infusion reaction. These 4 patients were analyzed in the efficacy evaluation as randomized, but in the safety evaluation in the monotherapy arm.

The baseline characteristics of the ITT population is shown in Table 12:

Table 12. Baseline Characteristics of the ITT Population

Characteristics	Cetuximab plus irinotecan (N=218)	Monotherapy (N=111)
Age (years)		
Median	59	58
Range	26-82	39-84
Gender, n (%)		
Male	143 (65.6)	63 (56.8%)
Female	75 (34.4%)	48 (43.2%)
Race, n (%)		
Caucasian	214 (98.2%)	323 (98.2%)
Black	2 (0.9%)	2 (0.6%)
Asian	2 (0.9%)	4 (1.2%)
KPS		
< 80	25 (11.5%)	15 (13.5%)
≥80	193 (88.5%)	96 (86.5%)

Baseline characteristics and KPS were similar in both arms. The study population contained a higher proportion of males and the great majority was of Caucasian race. Two-thirds of the randomized population had KPS ≥80.

The baseline tumor characteristics and prior treatment is shown is Table 13:

Table 13. Baseline Tumor Characteristics

Characteristics	ERBITUX plus irinotecan (N=218)	ERBITUX Monotherapy (N=111)
Site of primary:		
Colon	125 (57.3)	65 (58.6)
Rectum	90 (41.3)	43 (38.7)
Missing	3 (1.4)	3 (2.7)
No. Metastatic sites		
1	102 (46.8%)	62 (55.9%)
2	78 (35.8%)	27 (24.3%)
>2	9 (4.1%)	6 (5.4%)
Tumor sites		
Liver	153 (70.2%)	76 (68.5%)
Lung/Lymph node chest	71 (32.6%)	29 (26.1%)
Lymph node abdomen/pelvis	21 (9.6%)	16 (14.4%)
Intestine/visceral	3 (1.4%)	0 (0%)
Other	38 (17.4%)	13 (11.7%)
No. Previous Rx lines		
1	41 (18.8%)	27 (24.3%)
2	79 (36.2%)	41 (36.9%)
3	61 (28.0%)	20 (18.0%)
>3	37 (17.0%)	23 (20.7%)
Adjuvant therapy	59 (27.1%)	37 (33.3%)
Prior oxaliplatin	135 (61.9%)	71 (64.0%)

Primary tumor site, baseline tumor characteristics and previous chemotherapy treatment were well –balanced across the treatment arms. Approximately one third of the patients had previously failed adjuvant therapy and two-thirds of the patients had received prior oxaliplatin treatment.

In regards to the prior irinotecan regimen, 54.1% (178 patients) received 180 mg/m^2 once every two weeks, 26.7% (88 patients) received 350 mg/m^2 every 3 weeks and 16.1% (53 patients) received 125 mg/m^2 irinotecan weekly regimen. The best overall response to the most recent irinotecan-containing chemotherapy was partial remission in 23 (7%) patients.

The percentage of EGFr positive staining on tumor cells was also well balanced between the two arms, with results shown in Table 14.